REMARKS

Status of the Claims

Applicants respectfully acknowledge that the Examiner has deemed that claims 1-3 are free of the prior art and further that claims 1 and 3 would be allowable if the objection is obviated.

Claims 1-3 have been amended. Claims 1-3 have been amended to replace "Seq. Id. No." with --SEQ ID NO:-- as suggested by the Examiner to overcome an objection to these claims as discussed more fully below. In addition, claims 2 and 3 have been amended to correct some inadvertent typographical errors therein. For claim 2, a period has been inserted after the claim number in line 1. The period had been inadvertently omitted. In claim 3, the semicolon that immediately follows "4" has been replaced with a period to provide the correct form of punctuation.

Claims 4 and 5 have been added. The new claims, which depend from claim 2, are drawn to isolated proteins comprising an amino acid sequence having at least 90% or 95% sequence identity to the amino acid sequence set forth in SEQ ID NO: 3. Support for the new claims can be found in the specification, particularly on pages 15-16.

No new matter has been added by the amendments to the claims, or by the addition of the new claims.

Claims 1-5 are pending. Reexamination and reconsideration of the application as amended are respectfully requested.

The Sequence Listing Has Been Amended

The Office Action indicates that new paper and computer-readable forms of the sequence listing must be submitted because the specification recites sequences on page 29, lines 9, 12, and

20-21 without a sequence identifier or SEQ ID NO. The Office Action further indicates that the specification must be amended to include the SEQ ID NOs for these sequences.

The sequence listing and specification have been amended as required by the Examiner. The sequence listing has been amended to include the sequences recited on page 29 of the specification. New paper and computer-readable forms of the sequence listing and a statement that the contents of both forms are the same are included herewith. The specification has also been amended at page 29 to add the required sequence identifiers. No new matter has been added by the amendments to the sequence listing and specification.

The Objection to the Specification Should Be Withdrawn

The Examiner has objected to the specification because it contains embedded hyperlinks on, for example, page 10, lines 1 and 15. The Examiner indicates that hyperlinks and/or other forms of browser-executable code are not permitted under current USPTO policy and requires deletion of the embedded hyperlinks. Applicants have deleted the hyperlinks in the paragraph that bridges pages 9 and 10 and in the first complete paragraph on page 10. Accordingly, Applicants submit that the objection to the specification should be withdrawn.

In addition to the deletion of the hyperlinks, Applicants have also amended the specification to correct an inadvertent typographical error in the paragraph beginning at line 7 on page 20. The first sentence of this paragraph, which is drawn to variants of the Bs2 protein, incorrectly makes reference to the nucleotide sequence of Seq. ID No. 4. This sentence has been amended to correctly refer to the Bs2 amino acid sequence set forth in Seq. ID No. 3. To make this change, "4" has been replaced with --3-- at line 8 on page 20. No new matter has been added by way of amendment to the specification.

The Objection to the Claims Should Be Withdrawn

The Examiner has objected to claims 1-3 for reciting more than one period due to the usage of "Seq. ID No." in each of these claims. The Examiner has suggested that "Seq. ID No." be replaced in the claims with --SEQ ID NO:-- to overcome the objection. The Examiner is respectfully reminded, however, a claim may contain internal periods, if such periods are used for abbreviations, as is the case for claims 1-3. *See*, MPEP 608.01(m).

In the interest of placing the claims in a form ready for allowance and not to limit the scope of their claimed invention, Applicants have amended claims 1-3 to replace "Seq. Id. No." with --SEQ ID NO:--. In view of the claim amendments, the objections to the claims should be withdrawn. Furthermore, given that the Examiner has indicated that claims 1 and 3 would be allowable if the objection is obviated, Applicants submit that amended claims 1 and 3 should be allowed.

The Rejections of Claim 2 Under 35 U.S.C. § 112, First Paragraph, Should Be Withdrawn

Claim 2 has been rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. Claim 2 has been amended. Claims 4 and 5 have been added. This rejection is respectfully traversed.

In the Office Action, the Examiner indicates that the specification, while being enabled for the isolated protein comprising the amino acid sequence set forth SEQ ID NO: 3, does not reasonably provide enablement for a protein comprising an amino acid sequence having at least 85% sequence identity to SEQ ID NO: 3 and having Bs2 protein biological activity. The Examiner asserts that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope these claims. The Examiner cites the teachings of Lazar *et al.* and Broun *et al.* in support of the position that it is unpredictable as to whether any amino acid substitutions, additions, or deletions in a protein will retain the protein activity. The Examiner concludes that

in view of the breath of the claims, the lack of guidance, the unpredictability, the state of the art and the limiting working examples, undue trial and error would be required for one skilled in the art to obtain a protein having 85% sequence identity to SEQ ID NO: 3 and still having Bs2 biological activity.

First, in contrast to the Examiner's conclusions, sufficient guidance is provided in the specification to enable one of ordinary skill in the art to make and use the invention. Applicants have provided the amino acid sequence of SEQ ID NO: 3. The isolated proteins of the invention vary from SEQ ID NO: 3 by structural parameters (*e.g.*, percent amino acid sequence identity to SEQ ID NO:3). Guidance for determining percent sequence identity, for example, is provided in the specification on pages 9-10.

Moreover, the claimed proteins retain Bs2 protein biological activity and therefore encompass functional variants and fragments, including amino acid substitutions, deletions, truncations, and insertions. Guidance regarding alterations that allow a protein of the invention to retain Bs2 protein biological activity is also provided. See, for example, pages 17-20 for guidance on conservative substitutions of amino acids.

The Federal Circuit has repeatedly stated that enablement is not precluded by the necessity for some experimentation, so long as the experimentation needed to practice the invention is not undue. *In re Wands* 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Furthermore, a considerable amount of experimentation is permissible, if it is merely routine, or if the specification provides a reasonable amount of guidance in which the experimentation should proceed. *Id.*

Applicants stress that when evaluating the quantity of experimentation required, the court looks to the amount of experimentation required to practice a single embodiment of the invention, rather than the amount required to practice every embodiment of the invention. For example, in *Wands*, the claims at issue were drawn to immunoassay methods using any monoclonal antibody having a binding affinity for HbsAg of at least 10^{-9} M. The PTO had taken the position that the claim was not enabled as it would take undue experimentation to make

the monoclonal antibodies required for the assay. The Federal Circuit reversed, and held that the claims were enabled, as the amount of experimentation required to isolate monoclonal antibodies and screen for those having the correct affinity was not undue. *Id.* at 1407. Clearly, the Federal Circuit did not contemplate that every antibody useful in the methods of the claim must be identified. Rather, the court considered the amount of experimentation required to identify one or a few monoclonal antibodies having the required affinity. *See also, Johns Hopkins University v. Cellpro*, 931 F. Supp. 303, 324 (D. Del. 1996), *aff'd in part, vacated in part, & remanded*, 47 U.S.P.Q.2d 1705 (Fed. Cir. 1998) ("The specification need only enable one mode of making the claimed invention.").

In the instant case, the quantity of experimentation required to practice the invention amounts to two steps. The first step is to generate a protein comprising an amino acid sequence that has at least 85% identity to SEQ ID NO: 2. Methods of making variant proteins are known in the art and are set forth in the specification on pages 17-21. The second step is to assay the protein for Bs2 protein biological activity. Methods for determining Bs2 protein biological activity are provided in Examples 2 and 3 of the specification. *See*, pages 27-32 of the specification.

Contrary to the position of the Office Action, ample guidance is provided in the instant specification to allow one of ordinary skill in the art to identify additional proteins encompassed by claim 2 and the newly added claims. Consequently, the quantity of experimentation necessary and the amount of guidance presented in the specification is sufficient to enable the claimed proteins as set forth in claim 2. Accordingly, it is submitted that claim 2 is fully supported by the specification and that the rejection of claim 2 under 35 U.S.C. § 112, first paragraph, for lack of enablement should be withdrawn.

Claim 2 has been rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession

of the claimed invention. Claim 2 has been amended. Claims 4 and 5 have been added. This rejection is respectfully traversed.

In the Office Action, the Examiner asserts that the specification only describes the protein having the amino acid sequence of SEQ ID NO:3 encoded by a nucleotide sequence from *Capsicum annum*, and does not describe the structural, physical, and/or chemical properties for the claimed sequence, other than it has 85% sequence identity to the disclosed sequence. The Examiner asserts that, while the claim recites functional language, it is unclear if all proteins having at least 85% sequence identity to SEQ ID NO: 3 will exhibit the recited functional activity.

The Examiner is respectfully reminded that claim 2 is not drawn to all isolated proteins comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence set forth in SEQ ID NO: 3. Rather, claim 2 is drawn to isolated proteins which comprise: (1) an amino acid sequence having at least 85% sequence identity to the amino acid sequence set forth in SEQ ID NO: 3 and (2) Bs2 protein biological activity.

The Examiner asserts that no description of the structural, physical, and/or chemical properties for the claimed sequences is provided, other than that the sequences have 85% sequence identity to the disclosed sequence. However, the recitation of an amino acid sequence having at least 85% identity with the amino acid sequence set forth in SEQ ID NO: 3 is a very predictable structure of the isolated proteins encompassed by the claimed invention.

The Examiner is reminded, that the description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces. 66 Fed. Reg. 1099, 1106 (2000). Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the Applicants were in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. 66 Fed. Reg. 1099, 1106 (2000). Applicants submit that the knowledge and level of skill in the art would

allow a person of ordinary skill to envision the claimed invention, *i.e.*, an isolated protein having at least 85% sequence identity to the amino acid sequence set forth in SEQ ID NO: 3.

Furthermore, the description of a claimed genus can be by structure, formula, chemical name, or physical properties. *See Ex parte Maizel*, 27 U.S.P.Q.2d 1662, 1669 (Bd. Pat. App. & Interf. 1992) (citing *Amgen v. Chugai*, 927 F.2d 1200, 1206 (Fed. Cir. 1991)). A genus of DNAs may therefore be described by means of a recitation of a representative number of DNAs, defined by nucleotide sequence, falling within the scope of the genus, or by means of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1569 (Fed. Cir. 1997); *see also* Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, first paragraph, "Written Description" Requirement, 66 Fed. Reg. 1099, 1106 (2000). The recitation of a predictable structure — having at least 85% amino acid sequence identity with the amino acid sequence set forth in SEQ ID NO: 3 — is sufficient to satisfy the written description requirement.

An Applicant, however, may also rely upon functional characteristics in the description, provided there is a correlation between the function and structure of the claimed invention. *Id.* (citing *Lilly* at 1568). Claim 2 recites such a functional limitation. Specifically, claim 2 recites that the claimed isolated proteins comprise Bs2 protein biological activity; thereby providing a functional characterization of the sequences claimed in the genus.

Example 14 of the Revised Interim Written Description Guidelines is directed to a generic claim: a protein having at least 95% sequence identity to the sequence of SEQ ID NO:3, wherein the sequence catalyzes the reaction A → B. The Training Materials concludes that the generic claim of Example 14 is sufficiently described under § 112, first paragraph, because 1) "the single sequence disclosed in SEQ ID NO:3 is representative of the genus" and 2) the claim recites a limitation requiring the compound to catalyze the reaction from A → B. The Guidelines conclude that one of skill in art would recognize that the Applicants were in possession of the necessary common attributes possessed by the members of the genus.

Following the analysis of Example 14, Applicants submit that amended claims satisfy the written description requirements of § 112, first paragraph. Specifically, the claims of the present invention encompass isolated proteins comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence set forth in SEQ ID NO: 3, wherein said protein comprises Bs2 protein biological activity. As in Example 14, the specification discloses the amino acid sequence of SEQ ID NO:3, and claim 2 recites a limitation requiring the compound to have a specific function (*i.e.*, Bs2 protein biological activity).

Consequently, contrary to the Examiner's conclusion, the isolated proteins encompassed by claim 2 are defined by relevant identifying physical and chemical properties. In fact, the common attributes or features of the claimed isolated proteins are that they comprise Bs2 protein biological activity and have at least 85% amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO: 3.

In summary, the description of a representative number of species *does not* require the description to be of such specificity that it would provide individual support for each species that the genus embraces. Applicants submit that the relevant identifying physical and chemical properties of the disclosed genus would be clearly recognized by one of skill in the art and consequently, Applicants were in possession of the necessary common attributes or features of the elements possessed by the members of the genus. Accordingly, the rejection of the claim 2 under 35 U.S.C. §112, first paragraph, for lack of written description should be withdrawn.

In view of the amendment and remarks, it is submitted that the rejections under 35 U.S.C. § 112, first paragraph, should be withdrawn and not applied to the newly submitted claims.

CONCLUSIONS

In view of the above amendments and remarks, Applicants submit that the rejections of the claims under 35 U.S.C. § 112, first paragraph, are overcome. Applicants respectfully submit that this application is now in condition for allowance. Early notice to this effect is solicited.

If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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Nora C. Martinez

Version with Markings to Show Changes Made:

In The Specification:

Please amend the paragraph that begins at line 27 on page 9 and ends at line 3 on page 10 as follows:

The NCBI Basic Local Alignment Search Tool (BLAST) (Altschul *et al.*, 1990) is available from several sources, including the National Center for Biotechnology Information (NCBI, Bethesda, MID) and on the Internet, for use in connection with the sequence analysis programs blastp, blastn, blastx, tblastn and tblastx. [It can be accessed at http://www.ncbi.nlm.nih.gov/BLAST/. A description of how to determine sequence identity using this program is available at http://www.ncbi.nlm.nih.gov/BLAST/blast help.html.]

Please amend the paragraph that begins at line 4 on page 10 as follows:

Orthologs of the disclosed pepper Bs2 protein are typically characterized by possession of at least 50% sequence identity counted over the full length alignment with the amino acid sequence of pepper Bs2 using the NCBI Blast 2.0, gapped blastp set to default parameters. Proteins with even greater similarity to the reference sequences will show increasing percentage identities when assessed by this method, such as at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 90% or at least 95% sequence identity. When less than the entire sequence is being compared for sequence identity, homologs will typically possess at least 75% sequence identity over short windows of 10-20 amino acids, and may possess sequence identities of at least 85% or at least 90% or 95% depending on their similarity to the reference sequence. [Methods for determining sequence identity over such short windows are described at http://www.ncbi.nlm.nih.gov/BLAST/blast FAQs.html.] One of skill in the art will appreciate that these sequence identity ranges are provided for guidance only; it is entirely possible that

strongly significant homologs could be obtained that fall outside of the ranges provided. The present invention provides not only the peptide homologs are described above, but also nucleic acid molecules that encode such homologs.

Please amend the paragraph that begins at line 7 on page 20 as follows:

Variants of the Bs2 protein may also be defined in terms of their sequence identity with the prototype Bs2 protein shown in Seq. ID No. [4.] 3. As described above, Bs2 proteins have Bs2 biological activity and share at least 60% sequence identity with the pepper Bs2 protein. Nucleic acid sequences that encode such proteins may readily be determined simply by applying the genetic code to the amino acid sequence of a Bs2 protein, and such nucleic acid molecules may readily be produced by assembling oligonucleotides corresponding to portions of the sequence.

Please amend the paragraph that begins at line 6 on page 29 as follows:

To make these transient expression constructs using the *Bs2* gene, adapter primers containing an XbaI site were designed for PCR amplification of the 5' end of the *Bs2* gene. For the X5 construct, the primer was 5' CCTCTAGA**ATGGCTCATGCAAGTGTGCGTTCTCTTATG** 3' (SEQ ID NO: 10) (underlined sequence is the XbaI site, bolded sequence encodes the first 10 amino acids of Bs2). For the XO5 construct which includes the first intron located in the 5' UTR sequence, the primer was 5'CCTCTAGA**C**AAAATATTTCTTGGAGTGAATTTGA 3' (SEQ ID NO: 11) (underlined sequence is the XbaIsite, bolded letter is the transcriptional start site of *Bs2*). For both constructs the second primer used for amplification was 5' CCATCCCACACTTCACAACTCCA 3'[.] (SEQ ID NO: 12). Amplified products were cloned and sequenced to check fidelity of the clones. Clones for both constructs were digested with XbaI and SalI and ligated to pMD1 vector that had been digested with XbaI and SalI. The majority of the *Bs2* gene was isolated as a SalI-

EcoRI fragment from a cosmid that was cloned into pBluescript KS + (Stratagene, La Jolla, CA). The 3' ends of the two constructs were derived from PCR amplification of the appropriate 3' RACE product using the primers 5' GTCCTTGAGCGCCTCATG [3'and] 3' (SEQ ID NO: 13) and 5' ACTAAACTGGGTGTCTCATCGT 3'[.] (SEQ ID NO: 14). This PCR products was cloned into the pCRII-TOPO vector (Invitrogen, Carlsbad, CA) and sequenced to check the fidelity of the clone. The 3' end fragment was isolated by digesting the pCRII-TOPO clone with EcoRI and ligating the fragment to the SalI-EcoRI pBluescript KS + construct that had been digested with EcoRI. Proper orientation of the EcoRI 3' end fragment was determined by sequencing. This construct was digested with SalI and SacI (the SacIsite is in the plasmid polylinker) and ligated to the initial pMD1 constructs which had been digested with SalI and SacI, to produce the X5 and XO5 constructs.

In The Claims:

Please amend claims 1, 2 and 3 as follows:

1. (Amended) An isolated protein comprising the amino acid sequence set forth in [Seq. ID No.] SEQ ID NO: 3.

2. (Amended) An isolated protein comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence set forth in [Seq. ID No.] SEQ ID NO: 3, wherein said protein comprises Bs2 protein biological activity.

3. (Amended) An isolated protein encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of:

(a) the nucleotide sequence set forth in [Seq. ID No.] SEQ ID NO: 1;

(b) the nucleotide sequence set forth in [Seq. ID No.] SEQ ID NO: 2; and

(c) the nucleotide sequence set forth in [Seq. ID No.] SEQ ID NO: 4[;].